More precise dosing of acenocoumarol for better control in patients aged above 80 years, a randomised controlled pilot study

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Letter to the Editors-in-Chief

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ABSTRACT

Introduction: Many elderly patients are confined to treatment with vitamin K antagonists (VKA) instead of direct oral anticoagulants (DOACs). However, quality of VKA treatment declines with age. This might be caused by the lower dose requirements with increasing age, which result in relatively large day-by-day VKA dose differences. Therefore, more precise dosing with smaller dose increments might improve quality of VKA treatment in the elderly.

Methods: We randomised 80 elderly patients (≥80 years, using 0.5–2 mg acenocoumarol daily) to either conventional dosing with 1.0 mg acenocoumarol increments, or more precise dosing with 0.5 mg increments, to assess effect sizes and feasibility of a larger trial.
We compared changes in the time in therapeutic range (TTR), INR variability and anticoagulation-related quality of life (measured with the PACT-Q) between treatment groups.

Results: Overall, baseline TTR was 61.3 ± 19.2. After six study months, TTR had improved to 69.5 ± 19.7 in the precise dosing group versus 67.7 ± 21.2 in the conventional dosing group (absolute difference 3.4 (95% CI −6.7 to 13.6)). The between-groups difference in INR variability was not assessed because of baseline differences.
PACT-Q convenience declined slightly with more precise dosing, compared with conventional dosing: 2.1/100 (95% CI 0.5–3.7). Satisfaction decreased equally in both groups with −6.4 ± 8.6/100.
Four dosing errors occurred: three with precise and one with conventional dosing.

Conclusion: Although more precise dosing of acenocoumarol leads to a slightly higher TTR, this effect is too small to convey a relevant clinical benefit and could be abolished by the increased risk of medication errors.

Many elderly patients continue to use vitamin K antagonists (VKA) instead of direct oral anticoagulants (DOACs), because of contraindications such as kidney disease or interacting medication. However, the quality of VKA treatment declines with rising age; the time in therapeutic range (TTR) decreases, and the international normalised ratio (INR) variability increases [1]. Both increase bleeding and thrombotic risks [2,3].

At the same time, the required VKA dosage declines, as we showed previously: from 2.3 mg daily in patients aged 70–79, to 1.9 mg in those aged 80–89 and 1.6 mg acenocoumarol in those aged 90 or above [1]. These low doses of acenocoumarol, a drug only available in 1 mg tablets, cannot be spread evenly over the week. We hypothesised that more precise dosing, with smaller acenocoumarol increments, improves the quality and stability of anticoagulation in the elderly.

We performed an open-label, randomised controlled pilot study (EU Clinical Trials Register 2016-003086-25, protocol in Data S1) to determine the effect size for, and feasibility of, a full-scale trial. Patients from our first-line regional anticoagulation clinic were eligible if they were 80 years of age or above, used an average daily acenocoumarol dose between 0.5 and 2.0 mg for any indication, were expected to continue treatment for at least six months, and had started treatment over nine months ago (to allow a dose-finding period of at least three months before the six-month pre-study period). Eligible patients were informed about the study during regular monitoring appointments and could return a postcard to indicate their interest. Eighty patients provided informed consent and were enrolled: 40 were randomised to more precise dosing with 0.5 mg increments; the other 40 were allocated to continue their treatment with conventional dosing with 1.0 mg increments (Fig. 1). Randomisation was stratified by INR target range (2.0–3.0 or 2.5–3.5). All other aspects of treatment, including dosing algorithms and frequency of INR testing, were unchanged and performed as per usual care.

Over six months of study treatment, we calculated the TTR and INR variability, and compared them with the TTR and INR variability in the six months before study entry (pre-study period). We compared the changes in TTR and INR variability between the allocated treatment groups (intention to treat). TTR was calculated using the Rosendaal method [4]; INR variability was calculated following Fihn [5]:

$$\text{INR variability} = \sqrt{\frac{1}{n-1}\sum_{i=2}^{n}\frac{(\text{INR}_i - \text{INR}_{i-1})^2}{\Delta t\ (\text{days})}}$$

Additionally, we compared the impact on the anticoagulation-related quality of life by measuring the change in PACTQ [6] convenience and satisfaction after the six months of study treatment (intention to treat). We summarised the occurrence of medication errors by allocated treatment group.

Baseline characteristics and outcomes of the study are summarised in Table 1. Patients' age ranged from 80 to 96. During the pre-study period, acenocoumarol dosage was 1.4 ± 0.4 mg daily. Mean ± sd TTR was

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61.3% ± 19.2, comparable between treatment groups. Sixty-three (79%) patients used ≥5 medicines chronically, almost equally distributed in both treatment groups, indicating that co-morbidity was comparable in both groups. The indications for anticoagulation were well balanced in both treatment groups. Despite randomisation, patients allocated to more precise dosing had a higher INR variability than patients allocated to conventional dosing.

After the initiation of study treatment, two patients allocated to more precise dosing switched back to conventional dosing: one patient the day after randomisation because of social circumstances; the other 34 days after randomisation because of itching attributed to the study medication. One patient in the conventional dosing group suffered a fatal COPD exacerbation 88 days after randomisation.

Mean daily acenocoumarol dose did not change during the study, and was 1.3 ± 0.4 mg for the precise dosing and 1.4 ± 0.4 mg for the conventional dosing group.

Mean TTR improved significantly in both groups. The TTR improvement was slightly larger in the more precise dosing group: 3.4 (95% CI −6.7 to 13.6) percentage points, a difference that will only have a limited effect on bleeding and thrombotic risks [2].

Median INR variability slightly improved after the introduction of more precise dosing (difference −0.067 [−0.228–0.057]), while patients in the conventional dosing group somewhat increased in variability (difference 0.025 [−0.090–0.240]). However, this cannot be fully attributed to the more precise dosing, as patients with a higher baseline variability tended to stabilise, and those with lower INR variability tended to become more volatile, regardless of the allocated group (Spearman ρ −0.51).

More precise dosing affected quality of life. Patients in the more precise dosing group found their treatment slightly less convenient than patients in the conventional dosing group, with a difference of 2.1 (95% CI 0.5–3.7) on a 0–100 scale. We expected that patients would find their treatment more convenient if the number of tablets fluctuated less over the days. However, the higher number of tablets a patient had to take could also have made the treatment more burdensome. Furthermore, patients in the more precise dosing group felt more dependent on others: 8 out of 40 participants reported an increase in dependence of ≥2 points (dependence scored on a five-point scale), in contrast to only 1 out of 37 in the conventional dosing group. Interestingly, treatment satisfaction worsened equally in both groups: −6.4 ± 8.6. Especially the sense of reassurance as a result of the anticoagulation treatment decreased.

Table 1
Baseline characteristics and changes in quality of anticoagulation and quality of life.

Characteristic	More precise dosing (n = 40)	Conventional dosing (n = 40)
Demographics		
Age (years) - mean ± sd	84 ± 3	85 ± 4
Female - no. (%)	19 (48%)	16 (40%)
Polypharmacy - no. (%)	31 (78%)	32 (80%)
Anticoagulant treatment		
Indication - no. (%)		
AF	34 (85%)	33 (82%)
VTE	3 (8%)	2 (5%)
Valve	1 (2%)	2 (5%)
Other	2 (5%)	3 (8%)
INR target range - no. (%)		
2.0–3.0	36 (90%)	36 (90%)
2.5–3.5	4 (10%)	4 (10%)
Daily acenocoumarol dose (mg) - mean ± sd	1.3 ± 0.4	1.4 ± 0.4
Time in therapeutic range (%) – mean ± sd		
Pre-study period	60.5 ± 18.8	62.1 ± 19.7
Change during study treatment	9.0 ± 22.1	5.6 ± 23.4
Difference in change - pp. (95% CI)	3.4 (−6.7 to 13.6)	
INR variability - median [IQR]		
Pre-study period	0.31 [0.18–0.55]	0.23 [0.14–0.36]
Change during study treatment	−0.067 [−0.228–0.057]	0.025 [−0.090–0.240]
Anticoagulation-related quality of life		
Convenience - median [IQR]		
Pre-study period	98.1 [95.7–100.0]	98.1 [94.2–100.0]
Change during study treatment	−0.9 ± 3.7	1.2 ± 3.2[a]
Difference in change	−2.1 (−3.7 to −0.5)	
Satisfaction - median [IQR]		
Pre-study period	57.1 [53.6–64.3]	57.1 [52.7–65.2]
Change during study treatment	−6.4 ± 8.2	−6.5 ± 9.2[a]
Difference in change	0.1 (−3.9 to 4.0)	

Abbreviations: AF, atrial fibrillation; INR, international normalised ratio; VTE, venous thromboembolism.

[a] 3 patients missing because of death (1), brain tumour (1) and logistic reasons (1).

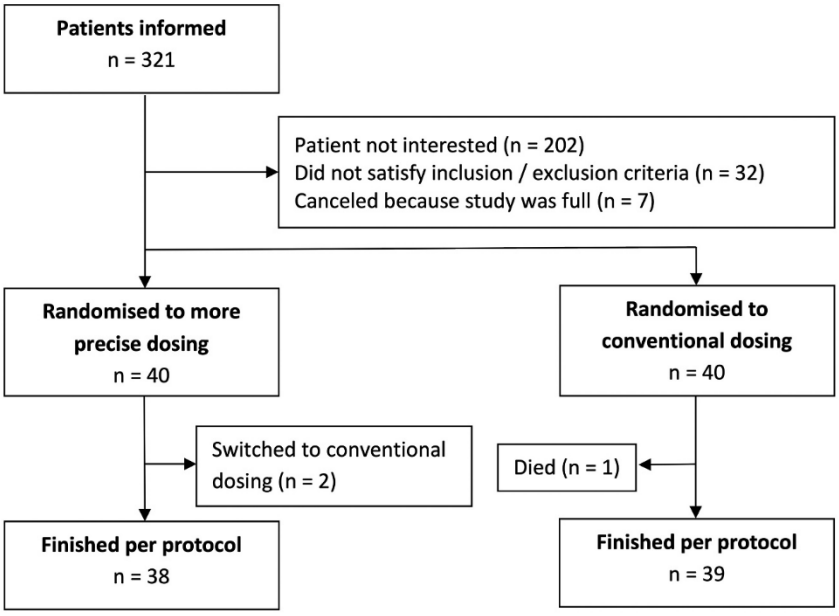

Fig. 1. Subject flow in the study.

Possibly, study participation, or the realisation that other treatments are available, had a negative effect on reassurance.

The use of unfamiliar acenocoumarol tablets led to medication errors. Four medication errors were registered in four subjects. Two patients in the more precise dosing group were given double doses of acenocoumarol during hospitalisation. Their maximum INRs in the 3 following weeks were 4.7 and 2.5. One patient took 1 mg tablets instead of the allocated 0.5 mg tablets at home during the last three study days, resulting in an INR of 5.9. One patient allocated to the conventional treatment group received a dosing schedule for 0.5 mg instead of 1 mg tablets during the first 14 days after inclusion; the INR rose to >12. The temporary elevated bleeding risks with these supratherapeutic INRs could abolish the small benefit of an improved TTR. However, no bleeding complications were reported in relation to any of the medication errors. If more precise dosing were to become more common, and physicians' experience with different concentrations per tablet grows, the increased risk of medication errors could diminish.

To our knowledge, we are the first to assess whether fine-tuning VKA dosing improves the quality of anticoagulation. Previous attempts to stabilise the VKA dose requirement by adding vitamin K resulted in a less day-to-day varied dose, a limited improvement of TTR, but not fewer complications [7]. Switching from short-acting acenocoumarol to longer-acting phenprocoumon resulted in a higher TTR and a lower INR variability [5,8]. However, the longer half-life slows interventions to lower the INR when needed.

Strengths of this study were the randomised and unintrusive setting; apart from two study visits, patients were monitored as usual. By offering home visits and study-medication delivery at home, we could also include the frailest patients and obtain a representative sample. A limitation was the small sample size, resulting in wide confidence intervals, inherent to the pilot nature of our study.

In conclusion: although more precise dosing of acenocoumarol leads to a slightly better TTR, this effect is probably too small to convey a relevant clinical benefit and seems not to outweigh the increased risk of medication errors. We will not proceed with a full-scale RCT.

CRediT authorship contribution statement

All authors were involved in the design of the study. Piersma-Wichers collected the data and was responsible for data handling. Van Miert supported the statistical analysis. Piersma-Wichers prepared the manuscript. All authors discussed the results, revised the manuscript critically, and approved submission of the manuscript.

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Declaration of competing interest

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Appendix A. Study protocol

The study protocol can be found online at https://doi.org/10.1016/j.thromres.2020.10.018.

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